



The Role of Traditional Medicinal Plants in Enhancing Antiretroviral Therapy for HIV

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ABSTRACT

The global burden of Human Immunodeficiency Virus (HIV) persists despite advances in antiretroviral therapy (ART), highlighting the urgent need for complementary strategies. Traditional medicinal plants (TMPs) have long been used in various cultures for disease management and are gaining renewed attention for their potential to enhance ART effectiveness. This paper explores the biochemistry of HIV infection, challenges posed by ART resistance and toxicity, and the mechanisms through which TMPs may act synergistically with ART to improve patient outcomes. A review of key plants, such as *Sutherlandia frutescens* and *Pelargonium sidoides*, illustrates promising antiviral and immunomodulatory properties. Phytochemicals from TMPs may inhibit viral replication, modulate host immune responses, and reduce drug toxicity. However, the integration of traditional medicine with conventional ART faces clinical, regulatory, and ethical challenges, necessitating rigorous research and standardized guidelines. This comprehensive examination underscores the importance of TMPs as potential allies in combating HIV/AIDS and enhancing the sustainability and efficacy of ART programs globally.

Keywords: Traditional Medicinal Plants (TMPs), Antiretroviral Therapy (ART), HIV/AIDS Management, Phytochemicals, Drug Resistance, Complementary Medicine, Herbal Remedies.

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a positive-strand RNA virus that belongs to the Lentivirus genus, part of the Retroviridae family. It infects CD4+ receptor-expressing cells (mainly T-cells, macrophages, and dendritic cells), particularly targeting CD4+ T-helper cells. This impairment of the immune system leads to increased vulnerability to opportunistic infections and cancers, causing HIV-related diseases like Acquired Immunodeficiency Syndrome (AIDS). Without treatment, untreated HIV progresses to immunodeficiency and often results in death. Drug-resistant strains of HIV-1 pose significant challenges in effective anti-retroviral therapy. Therefore, ongoing research into HIV-1's biochemistry and associated proteins, as well as novel anti-HIV compounds, is essential. Plant extracts are promising as they offer diverse chemical compounds that can lead to new anti-HIV drug candidates. Antiretroviral therapy (ART) plays a crucial role in enhancing the lives of those with HIV. Combining drugs in ART effectively reduces plasma viral load and curtails disease progression while improving quality of life for AIDS patients. Nevertheless, current ART drugs present several drawbacks, including drug resistance, toxicity, varying effectiveness, and potential long-term side effects like organ failure. Concerns about HIV resistance to anti-retroviral treatments highlight the urgent need for alternative anti-HIV agents. Research into natural products with different mechanisms of action has been undertaken for their potential anti-HIV activity in laboratory and clinical settings [1, 2].

Overview of HIV and Antiretroviral Therapy

Human Immunodeficiency Virus (HIV) causes acquired immunodeficiency syndrome (AIDS), a chronic disease with complex pathology from interactions with host cells. HIV targets CD4-positive T lymphocytes (TH cells), essential in regulating the immune response by producing cytokines. Similar to a hacker infiltrating a computer network, HIV infects TH cells, vital for recognizing and eliminating pathogens. Inside these cells, HIV proteins are improperly displayed on the surface, leading the immune system to mistakenly treat them as dysregulated, causing excessive non-specific cytokine release (TNF- α , IFN- γ , IL-1 β , IL-12, IL-15, IL-18). While this response aims to eliminate the infection, it leads to chronic inflammation due to the recruitment of additional TH cells. Antiretroviral therapy (ART) effectively treats HIV, improving life for those affected. Standard ART includes a mix of protease inhibitors, reverse transcriptase inhibitors, and integrase strand transfer inhibitors that target various stages of the HIV replication cycle to suppress it and slow disease progression. Despite its success, ART carries disadvantages, notably the potential for HIV to develop resistance to treatment, a concern documented by numerous research labs over decades as HIV adapts and escapes current therapies. [3, 4].

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Traditional Medicinal Plants: A Historical Perspective

In the UK, 2 million people are currently living with HIV infection, with sub-Saharan Africa being the most affected region worldwide. In 1986, the first isolations of HIV from AIDS patients finally confirmed the cause of HIV/AIDS, pronounced as the worldwide epidemic of the 20th century. Anti-retroviral therapy (ART) is an effective treatment for people living with HIV. The standard treatment, which entails a fixed-dose combination therapy of three anti-retroviral agents, was ARV, AZT, and EFV. These are taken daily for life, and adherence usually results in undetectable viral loads and normal CD4 counts, which significantly decrease morbidity and mortality. ART is significant in improving the life of people living with HIV; however, the drugs have many disadvantages, including but not limited to resistance, toxicity, limited availability, and a lack of curative effect. The potential for HIV to become resistant to anti-retroviral treatment has become an increasing concern. These shortcomings open avenues for the use of natural products to manage HIV/AIDS. Such natural products may already be known for mino-tions for a variety of things or for ethnomedical uses. UNESCO recognized around 3000 traditional medicinal plants (TMPs) that have been used for many generations to prevent and treat diseases. Demand for TMPs is increasing, particularly in Africa, where around 80% of the population depends primarily on plant-based medicines. Herbal medicine is accessible and non-controversial compared to modern medicine. TMPs relieved symptoms associated with HIV/AIDS or improved the effectiveness of ART in some cultures. Programs have been developed to study the safety and effectiveness of TMPs in clinical and population settings. Some of this work was aimed at identifying phytochemicals in TMPs that are active against HIV. Phytochemical extracts from TMPs that are traditionally used to treat symptoms associated with HIV/AIDS were screened for anti-HIV activity. Uninfected cells and cells infected with HIV-1 were treated with selected TMPs, and cell viability was examined. The selected TMPs consisted of Folklore- and South African TMPs reported to relieve various HIV/AIDS-associated symptoms [5, 6].

Mechanisms of Action of Antiretroviral Drugs

Antiviral drugs developed to inhibit HIV have targeted mainly three essential viral proteins post-entry: reverse transcriptase (RT), integrase (INT), and protease (PR). Although actions are directed to the viral proteins, the cellular supply of nucleoside triphosphates and the cellular proteolytic environment are necessary for their action. Exploiting these unique viral targets has proved to be an effective strategy for drug development. Nevertheless, the excellent HIV-1 titer and an elevated mutation rate soon render some of these antiviral compounds unusable in vivo. Cellular factors have been identified that, when unregulated, reduced the level of infection by a variety of viruses including HIV by modulating inflammation and the immune response. Plant-based remedy searches for possible new antiviral medicines are ongoing to identify novel antiviral targets against viruses including HIV, which are still being actively pursued. Anti-HIV candidate drugs must be screened for their anti-HIV as well as medicinal activity prior to determining their mechanisms of action. The bioavailability of the putative agent and the pharmacodynamics under consideration of its toxicology are additional requirements for clinical trial recommendation. These are dealt with in subsequent sections, focusing on compounds that can modulate cellular factors involved in the replication of HIV. A clear and accurate understanding of the unique viral structure and life cycle events is needed to fully understand how newly developed drugs can safely and effectively target HIV. HIV-1 exists in a non-infectious and voraciously infectious conformation (Env+ and Env-, respectively) and secreted as a virion with an external lipid membrane and proteins (gp120 and

gp41) critical for host cell binding and infection. A spherical and well-defined core is present that consists mainly of elicited p24 proteins within which a linear positive single strand of RNA genome and essential molecular brokers, i.e., RT, PR, and INT, are retained. The genome consists of three major genes, *env*, *gag*, and *pol* that encode the major structural components [7, 8].

Synergistic Effects of Traditional Plants and Antiretroviral Therapy

The synthetic anti-retroviral (ARV) drugs such as nevirapine (NVP), efavirenz (EFV) along with two nucleoside reverse transcriptase inhibitors (NRTI) backbone combinations developed during the last 2–3 decades to treat HIV/AIDS has significantly reduced morbidity and mortality associated with HIV infection. Though HAART effectively suppresses the virus proliferation from blood stream, it doesn't eradicate HIV-1 from the body and HIV-1 plays an active role even in the presence of therapy. Even with good adherence to potent ART, HIV-1 is able to either persist or recrudescence in latently infected CD4+ T cells, which can trigger de novo Viral Outgrowth in weeks to months after HAART interruption. Indications are that DDI or DDC exposure in patients with multi-drug-resistant HIV-1 (MDR-HIV) provides an excellent selection pressure for virulence albeit various cellular factors associated with HIV-1 but some factors are modulated by plant substances leading to the inhibition of wild type and mutant strains of the virus on continued treatment. Medicinal Plants are an important source of novel compounds with antiviral, antiprotozoal, anti-mycobacterial and anti-influenza properties, some of which inhibit enzymes involved in HIV replication but the effect of herbs on HIV-1 or HAART drugs in the response of HIV-1 to DDI or DDC treatment is selectively inhibited and absence of toxicity towards non-infected cells is desirable. HIV infected patients while on HAART often take herbal remedies for various reasons and, among the herbal remedies, plants such as *Papaver somniferum* contain opium that interfere with HAART metabolism and toxicity but certain plants that enhance HAART therapeutic efficacy without interfering with drug metabolism and toxicity exist too. As HIV/AIDS has high prevalence and morbidity/mortality in resource-constrained countries, NVP and EFV-based HAART is often initiated in HIV infected patients in Sub-Saharan Africa. Many herbal medicines are widely used in these settings and a powerful open access online database was constructed and is currently hosted by bioinformatics scientists where already documented anti HIV compounds in plants or their immune modulators are being searched in hope to be translated into six local languages for awareness generation among villagers [9, 10].

Key Traditional Medicinal Plants Used in HIV Treatment

The need for alternative medicinal plants for managing HIV/AIDS has renewed interest in traditional herbal medicines. Various plants have been traditionally used in Africa, particularly in South Africa (SA). *Sutherlandia frutescens* is among the most researched, with reported biological activities. Acetone and methanol extracts of *S. frutescens* showed potent anti-HIV activity, exceeding that of HAART, without reducing cell viability. Other plants like *Platanus alstonii* and *P. oxyphyllum* are reported to treat HIV/AIDS, tumors, and hypertension, with several extracts studied for their active components. Compounds with anti-HIV activity have been isolated from various *Pelargonium* species native to South Africa and Namibia, notably 4-methoxybenzyl ferulate. *P. sidoides* and *P. reniforme* were extensively studied, showing inhibitory effects on HIV replication and low cytotoxicity in cell lines. Concentrations above 20 µg/mL were necessary to see significant cytotoxicity in CB-4 cells. Additionally, *Eucalyptus* is widely used in SA for ailments, including HIV/AIDS. Recent studies indicate that *Eucalyptus* extracts inhibit *Bacillus subtilis* at high concentrations, suggesting potential for isolating effective metabolites against viruses, supporting its medicinal claims [11, 12].

Phytochemicals and Their Role in HIV Management

HIV/AIDS is one of the deadliest diseases in the world, affecting millions of patients and resulting in numerous deaths. Acquired immunodeficiency syndrome is a disease caused by infection with the human immunodeficiency virus (HIV), which leads to a gradual destruction of CD4+ T-cells and impairment of humoral and cellular immunity. The immune system defects that develop in HIV infected individuals are responsible for life-threatening opportunistic infections, malignancies, and neurological disturbances, ultimately leading to death. Currently, there is no vaccine available for the treatment of HIV/AIDS; however, highly active antiretroviral therapy (HAART) is currently the most widely used treatment regimen for HIV/AIDS. It functions mainly by inhibiting reverse transcriptase, protease, and integrase. But, due to the rapid mutation rates and selective pressure of the treatment itself, HAART regimens fail over time. One of the main problems of HAART treatment is that the currently available drugs only act on a specific phase of the viral life cycle and provide control of viral replication rather than eradication of

the virus from the body. Hence, traditional medicinal plants that show anti-HIV activity through different mechanisms of action can be used as complementary therapies in the treatment of HIV/AIDS. Moreover, the present review summarizes various natural products obtained from plants that exhibit significant anti-HIV effects through the above-mentioned mechanisms. Traditional medicine represents the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures in the preservation of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illness. Indigenous people have used plants for thousands of years for the treatment and management of diseases. Additionally, the ethnomedicine approach is a valuable tool in discovering and developing new bioactive drugs for modern medicine. Traditional medicinal plants used for HIV/AIDS management in Botswana and Eswatini are reviewed to consolidate the information available for further research in their contribution to HIV management [13, 14].

Clinical Studies on Traditional Plants And HIV

The search for effective anti-HIV agents, particularly targeting HIV-1 reverse transcriptase, is crucial given the rise of viral resistance. Strong activity against HIV-1 reverse transcriptase was shown by several tropane alkaloids derived from *Capparis tomentosa*, including 6 β -hydroxy-3 α -(β -hydroxy-3,3-dimethyl-pentyl)-8 β -azabicyclo[3.2.1]octan-7-one and corydaldine, along with others such as 3-phenyl-acrylic acid and 1-phenyl-ethylamine. Notably, [3-benzyl-4-hydroxy-coumarin and 2-O-Methyl-tropanes demonstrated strong inhibition of HIV-1 protease, with IC₅₀ values indicating significant deactivation of enzyme monomers. The impact of herbal traditional medicines (HTMs) containing *Prunella vulgaris* and *Crataegus pinnatifida* on the pharmacokinetics of nevirapine and efavirenz was assessed. Treatment with HTMs (30 g/day for 14 days) resulted in reduced AUC/geometric mean C_{max} for these anti-AIDS drugs, potentially leading to decreased antiviral effectiveness and treatment failure. Caution is advised when using HTMs alongside nevirapine or efavirenz. The interaction of the Chinese herbal medicine Chuan-Chi-Chiao with efavirenz on both uninfected and HIV-1-infected H9 lymphocytes showed that CC upregulated CYP3A4 isoform activity in uninfected cells and lowered EFV levels in infected cells, indicating the importance of monitoring herb use in patients on EFV to maintain therapeutic efficacy.

Challenges In Integrating Traditional Medicine with Antiretroviral Therapy

Over the past decade, the South African government has undertaken several efforts to promote the integration of traditional and complementary medicine into healthcare. Traditional medicines, however, pose challenges as they often do not undergo quality control mechanisms, and their efficacy and safety have not been empirically evaluated. Subsequently, there seems to be a large gap between the integration of traditional healing with ART. The HIV pandemic has affected global epidemics and resulted in a dozen deaths daily. The advent of ART has heralded a new era in the treatment of HIV infection. ART has many benefits, including increased life expectancy and productivity, reduced stigma, and overall improved well-being; however, there are concerns regarding adherence to the therapy. Factors that may lead to variable or inconsistent ART adherence include depression, stigma, alcohol abuse, unemployment, and the use of traditional medicine, among others. There is limited empirical evidence to support the different biobehavioral mechanisms underlying the interaction of antiretrovirals with the use of TM (henceforth TM). A variety of a priori pathways through which TM use may hamper retention in care or adherence to ART have been mentioned in several studies. These are divided into social mechanisms, healthcare provider mechanisms, patient mechanisms, and TM product mechanisms. Sociocultural beliefs, training, and prior experiences of TM healers and healthcare providers may hamper the translation of biomedical messages. In turn, patients' beliefs regarding the nature of the illness and how best to address it, as well as the risk of mistrust, may limit disclosure. Likewise, TM products may affect adherence by having a neurotoxic effect, reducing ART blood concentration, or causing food-drug interactions. Given South Africa's pluralistic healthcare environment, the importance of considering TM use in developing interventions to enhance adherence is emphasized. Consequently, this calls for in-depth explorations of how TM is used regarding ART in adults with HIV. TM is highly prevalent amongst patients with HIV, enabling a holistic view of the patients' treatment journey translated through emotion-mind-body-spirit interconnections. Nevertheless, there is a dearth of research employing qualitative methodologies that 'connect' the usage and context attendant to the use of TM with adherence [15, 16].

Regulatory and Ethical Considerations

To intensify ARV drugs' effectiveness, access to the ART medications must be adequately regulated through legislation, education, and communication health impasses must be addressed. Grassroots level

intervention or community sensitization and mobilization on the local medicinal plants' application will enhance accessibility to ARV plants. Information on the native ethnobotanical plants and conduct sensitizations on the 1st and the 2nd-hand use of HIV/AIDS novel local research and processing products for accessing ART alternatives to intoxicated pharmaceutical drugs & freon substances from general shops addiction. Core regulatory authorities, proper divisions, and association of field specialists in the health sector to design systematic records on the ART efficiency, mortality, morbidity collection and management strategy for the improvement of the therapy nationwide. Laboratory experts, testing consumables procurement, maintenance, and recycling strategy, Standard Operating Procedure manual compilation, and overall work strategies on laboratory activations on herbal Ethics and Guidelines, and their appropriateness for the communities must be defined. Research must provide adequate production consumables to develop the production technologies for large-scale and affordable commercial production, and its accessibility must be made general on workplace access [17, 18].

Patient Perspectives on Traditional Medicine

Patients with HIV and related opportunistic infections in South Africa often seek care from traditional health practitioners (THPs), who are diverse and include herbalists, religious healers, and "neuropathic" healers. Many THPs are well-respected in their communities and earn incomes comparable to medical doctors. They primarily use phyto-remedies, favoring single plant prescriptions while also utilizing combinations when necessary. The curative potential of these remedies often relies on the interaction of multiple plant components, enhancing pharmacological effects. To address gaps in mainstream healthcare, THPs utilize modern techniques for client education and care provision, sometimes alongside biomedically trained professionals, with no recorded instances of herbal overdose or decreased adherence to antiretroviral therapy (ART). Despite a growing appreciation for THPs' roles, biases persist toward biomedically trained practitioners. While THPs often possess a knowledge level equivalent to a medical diploma, both types of healers have limited retention of their training and experience, averaging around ten years since qualification. Differences in medical training breed cultural mistrust between various practitioners, leading to skepticism regarding THPs despite evidence supporting many African medicinal remedies. Expertise in HIV management isn't exclusive to biomedically trained clinicians. The relationship between a patient's self-concept, illness beliefs, and care providers underscores a need for collaboration between traditional and biomedical practitioners. Bridging the divide between their respective knowledge bases and establishing standardized care practices could foster a more holistic healthcare system [19, 20].

Cultural Implications of Using Traditional Medicinal Plants

The Kabarole District in western Uganda is home to more than 20 traditional herbalists. The majority of HIV-positive patients in western Uganda use herbal and herbal remedies to treat their diseases. While evidence supports the understanding of HIV and AIDS in Western Uganda, cultural beliefs influence the acceptance of Western medicine. There was widespread belief that cleansing and purifying agents (food and herbs) were the reasons that some HIV-positive patients lived many years despite the diagnosis. Traditional herbalists claimed to cure HIV/AIDS using herbs, roots, and plants growing in Kabarole District. In Kabarole District, the AIDS epidemic significantly changed local spiritual beliefs. Before the AIDS epidemic, Bujju, the dwarf god, was believed to be the cause of many diseases. Early in the AIDS epidemic, AIDS was blamed on the God of the Hill, the mighty sprinkle. This god punished women who broke the sanctity of marriage or engaged in adultery. The God of the Hill was associated with cholera, and the local shrub *Kijugujugu* and *Cassia occidentalis* were used as a cleansing agent to purify. Before the advent of AIDS, faeces in people's bush and armpits, which was believed to be the source of diseases, received attention. Faeces were originally believed to be the source of many ailments. Herbalists claimed to expel faeces and curses from a patient's body using purging agents and food. Until the recent advent of ELISA tests, many believed that the cause of HIV was food and eating habits. To treat the disease, foods were recommended that were said to be difficult to digest. Extensive past and recent experience with herbalists aged greater than 50 years led to the knowledge of many native plants. Some curative plants, such as cassava, which are thought to be incapable of causing HIV, hence the sarcastic saying that a pregnant woman cannot pass on the disease to the child via cassava, became the target of new accusations [21, 22].

Future Directions in Research

The combination of phytotherapy and antiretroviral treatment (ART) is increasingly important to address the limitations of ART alone in overcoming HIV and opportunistic infections. Utilizing

antimicrobial herbs from traditional medicine as adjuncts to ART is a promising strategy. Despite extensive HIV-1 research, challenges persist. Current drugs targeting various stages of the HIV-1 lifecycle face issues such as viral mutations impacting entry inhibitors and ongoing drug resistance concerns, especially in resource-limited areas. This highlights the urgent need for affordable therapeutic options. Drug resistance mutations affect both protease inhibitors and integrase inhibitors, which are often slow-acting. Infected individuals may seek folk medicine, but its efficacy in slowing disease progression requires thorough investigation. Traditional medicine offers potential candidates for chronic viral diseases, including HIV-1. Medicinal plants may provide curative agents for primary therapy and therapeutic options against drug-resistant HIV strains. Thus, screening these plants for efficacy against HIV-1 replication and potential anti-HIV-1 activity is necessary. The rise in multi-resistant HIV-1 strains complicates ART, leading to the search for alternative agents in traditional medicine. Comprehensive analyses of natural products against standard HIV-1 strains are crucial, with phylogenetic trees based on protein affinity and phylogeneticity guiding this research direction [23, 24].

Case Studies of Successful Integration

In Africa, traditional medicine is widely recognized and practiced, differentiating itself from modern medicine through its cultural knowledge and practices. It serves for diagnosis, prevention, and treatment of various conditions, with one key aspect being the therapeutic use of plants, which has led to the discovery of many anti-HIV substances. In rural areas lacking access to modern healthcare, traditional healers are often the first consulted due to their personalized approach that considers social and spiritual factors. While developed countries see a decline in herbal medicine use, developing nations continue to rely on it heavily. Zambia, facing a significant shortage of healthcare personnel, illustrates this dual healthcare system with traditional healers outnumbering doctors [25, 26, 27, 28]. The Traditional Health Practitioners Association in Zambia has over 40,000 registered members, compared to just 1,000 conventional medical doctors, creating a doctor-to-population ratio of 1 to 17,589 against the ideal of 1 to 5,000. This imbalance poses financial challenges for public healthcare facilities. Amidst the lack of healthcare providers, traditional healers play a crucial role in managing HIV/AIDS opportunistic diseases. Reports show that 75% of in-patients and 68% of individuals seeking HIV counseling use traditional medicines, often due to constraints in accessing antiretroviral therapy (ART). However, knowledge on specific plants for treating these conditions remains limited. This paper discusses the medicinal plants used for managing HIV/AIDS opportunistic infections in Livingstone, Southern Province, Zambia [29, 30, 31, 32, 33, 34].

Global Perspectives on Traditional Medicine and HIV

Sub-Saharan Africa has the highest number of HIV infections globally, with about 5.9 million people affected, and is also the most impacted by TB, recording 1.1 million new cases and around 480,000 individuals co-infected with both diseases. Antiretroviral therapy (ART) began in South Africa in 1997 and has significantly increased since. The nation aligns with the 2015 WHO recommendations and the 2021 HIV, TB, and STIs National Strategic Plan (NSP), stressing the importance of partnerships. Issues such as community participation, key populations, and stigma are central to implementing programs for targeted populations [33, 34, 35, 36]. In South Africa, 1,692 public-sector facilities offer ART, primarily through primary healthcare clinics supported by non-governmental organizations. Among HIV-positive females, about 39% reportedly use AHERs daily, raising concerns about effective HIV care and public health implications based on potential interactions of the agents used. The historical role of traditional healers was pivotal, with studies on their practices dating back to 1930. With the introduction of synthetic drugs during the 'golden age' of Western medicine, traditional healers were often marginalized and viewed as primitive. However, the HIV and TB crises highlight the need to reassess the contributions of these healers, as South Africa is home to approximately 300,000 traditional healers, with an estimated 70% of the population consulting them as a primary healthcare resource for HIV and TB treatment [27, 28].

CONCLUSION

Traditional medicinal plants offer significant promise as complementary agents to antiretroviral therapy in the management of HIV/AIDS. Their rich phytochemical diversity provides mechanisms to inhibit viral replication, support immune function, and potentially overcome some limitations of ART, such as drug resistance and side effects. Plants like *Sutherlandia frutescens* and *Pelargonium sidoides* exemplify how traditional knowledge and modern scientific inquiry can intersect to reveal new therapeutic avenues.

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Nonetheless, integrating TMPs with ART presents challenges, including the need for rigorous clinical validation, standardization, and monitoring of herb-drug interactions. Ethical considerations, regulatory frameworks, and community-based strategies are critical to ensuring the safe and effective use of traditional medicine in HIV care. Future research should aim at systematically exploring TMPs' potential, fostering a holistic approach that enhances ART efficacy while respecting cultural practices and promoting global health equity.

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